

Appl. No. : 10/534,825  
Confirmation No. : 8880  
Applicant : David Edwin Thurston, et al.

Filed : October 20, 2005  
Title : Pyrrolobenzodiazepines

TC/A.U. : 1624  
Examiner : Bruck Kifle

Docket No. : 065435-9048-US00

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Mail Stop AF  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**DECLARATION UNDER 37 C.F.R. 1.132**

I, Dr. Philip Howard, declare as follows:

1. I have personal knowledge of the following facts and I make this declaration in support of the prosecution of U.S. Patent Application Serial No. 10/54,825 before the United States Patent and Trademark Office.

2. I am currently employed Vice-President (Chemistry) at SpiroGen Limited, a position I have held since June 2003 (full time). Prior to that I was employed as Senior Research Officer, University of London, School of Pharmacy.

3. My curriculum vitae is attached as Appendix A.

4. I am a co-inventor of the subject matter of the above-identified application and I am familiar with the art and with the prosecution history of this application.

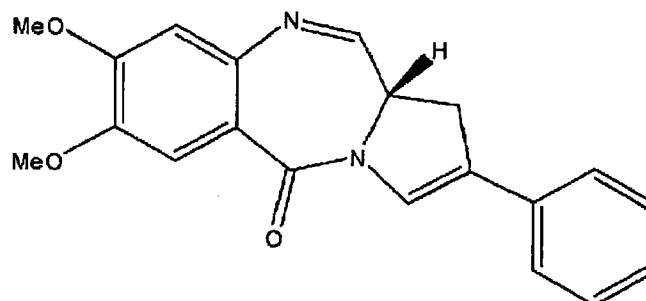
5. We have now performed additional comparative testing between the compounds of the present invention and the prior art compounds.

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Amdt. dated September 4, 2007

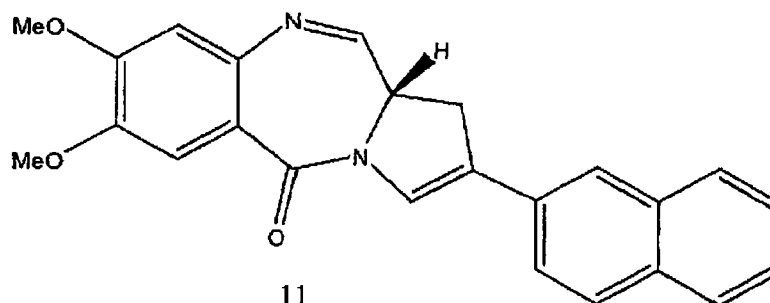
Reply to Office action of March 2, 2007

6. The compounds tested were



C1

from the prior art and



11

according to the present invention.

7. The compounds were tested according to the assays described in the specification at pages 61-62.

8. The results are shown in the table below.

	IC <sub>50</sub> (nM) Breast MACL MCF7	IC <sub>50</sub> (nM) Renal RXF944L	IC <sub>50</sub> (nM) Lung 629L	IC <sub>50</sub> (nM) Melanoma MEXF462NL
C1	19.33	20.50	44.50	40.00
11	0.22	1.32	6.50	1.80

9. The data shows considerable improvement across a range of cell lines in the activity of compound 11 over compound C1, wherein the only change is in the 2-substituent from phenyl to naphthyl.

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10. I hereby declare that all statements made herein of my own knowledge are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated this 31 day of AUGUST, 2007.

  
\_\_\_\_\_  
Dr. Philip Howard

**Name:** Dr Philip Wilson Howard  
**DOB:** 24/6/1964  
**Age:** 42  
**Nationality:** British  
**Sex:** Male  
**Current Position:** Director of Chemistry Spirogen Senior Research Fellow,  
Deputy Director CR-UK Gene Targeted Drug Design  
Research Group

**Qualifications:**

BSc (2.1) Applied Chemistry, Kingston Polytechnic  
PhD University of East Anglia, "The preparation and  
Chemistry of Dihydrocatechol Derived Organoiron  
Complexes".

**Career:**

1991-1994 Post Doctoral Fellow, SmithKline Beecham  
1994-1995 Post Doctoral Fellow, University of  
Portsmouth  
1995-2000 Senior Lecturer, University of Portsmouth  
2000-2001 Senior Research Fellow, University of  
Nottingham  
2001-Director of Chemistry Spirogen/Senior Research  
Fellow ULSOP.

**Grants:**

CR-UK Programme Grant C180/A1060 (Co-PI)  
CR-UK Project Grant C180/A1066 (Co-PI)  
CR-UK Programme Grant C180/A5068 (Co-PI)  
CR-UK Studentship C180/A4522 (Co-PI)  
CR-UK Studentship C180/A2778 (Co-PI)  
EPSRC Case Award GR/PO1366/01 (Co-PI)  
EPSRC Case Award  
PSRC Quota Award  
CR-UK Equipment Grant C180/A3959 (Co-PI)

**Publications/patents:** Over 40 papers in peer reviewed scientific journals  
and over 14 patents (see below)

**Invited Lectures:**

SMi Drug Design, "Gene Targeting Approaches to Anti-  
Cancer Drug Design", London, UK (February 2003).

Societa Chimica Italiana Divisione Di Chimica Farmaceutica  
(Italian Medicinal Chemistry Summer School), Urbino, Italy  
(Jun-Jul 2003).

The Royal Society of Chemistry – Cancer Therapeutics in the  
21st Century, Manchester, UK (October 2003).

25th Winter Meeting of the EORTC-PAMM Group, Bradford, UK (January 2004).

Part 1 of SMI's Global Cancer Event - Innovations in Cancer Drug Discovery, "Design of Small Sequence-Selective DNA-Interactive Molecules", London, UK (June, 2004).

British Association of Cancer Research, Oxford, UK.

## Publications and Patents

### Papers

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Chen, Zhizhi; Gregson, Stephen J.; Howard, Philip W.; Thurston, David E. **A novel approach to the synthesis of cytotoxic C2-C3 unsaturated pyrrolo[2,1-c]benzodiazepines (PBDs) with conjugated acrylyl C2-substituents.** *Bioorganic & Medicinal Chemistry Letters* (2004), 14(6), 1547-1549. CODEN: BMCLE8 ISSN:0960-894X. CAN 140:406790 AN 2004:189175 CAPLUS (Copyright

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Masterson, Luke A.; Croker, Stephen J.; Jenkins, Terence C.; Howard, Philip W.; Thurston, David E. **Synthesis and biological evaluation of pyrrolo[2,1-c][1,4]benzodiazepine (PBD) C8 cyclic amine conjugates.** *Bioorganic & Medicinal Chemistry Letters* (2004), 14(4), 901-904. CODEN: BMCLE8 ISSN:0960-894X. CAN 140:321339 AN 2004:99276 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

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Wilson, Stuart C.; Howard, Philip W.; Thurston, David E. **Design and synthesis of a novel epoxide-containing pyrrolo[2,1-c][1,4]benzodiazepine (PBD) via a new cyclization procedure.** *Tetrahedron Letters* (1995), 36(35), 6333-6. CODEN: TELEAY ISSN:0040-4039. CAN 124:8772 AN 1995:786320 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

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## Patents

Howard, Philip Wilson; Gregson, Stephen John; Taylor, Peter William; Thurston, David Edwin; Hadjivassileva, Tsveta Stepanova. **Preparation, DNA crosslinking reactivity, antitumor and antibacterial activity of pyrrolobenzodiazepine dimers.** PCT Int. Appl. (2005), 62 pp. CODEN: PIXXD2 WO 2005085260 A1 20050915 CAN 143:306350 AN 2005:1004755 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

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**the treatment of proliferative diseases.** PCT Int. Appl. (2005), 108 pp. CODEN: PIXXD2 WO 2005085250 A1 20050915 CAN 143:306347 AN 2005:1004747 CAPLUS (Copyright (C) 2006 ACS on SciFinder (R))

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